merely in bringing out the association between a series of obscure and puzzling symptoms developed in the course of several years, which finally seem to have found explanation in the cancerous growth revealed well toward the end of the series.

W J McGEE[1]

REVERSIBLE CHANGES IN PERMEABILITY PRODUCED BY ELECTROLYTES

ACCORDING to one opinion permeability is a relatively fixed property of the cell and is altered only as the result of injury: the alteration is then irreversible.

Another view assumes that there are reversible changes in permeability which involve no injury and which may form a normal part of the activities of the cell. If such changes occur it is clear that they may control the course of metabolism. That permeability may be altered in this manner is suggested by a number of facts,[1] but their interpretation is too doubtful to place this view on a firm basis. It is highly important that its truth or falsity be established by rigorous proof. Such proof seems to be afforded by a series of experiments, some of which are described below.

The method pursued in these experiments has been described in a previous paper.[2] It consists in cutting disks of living tissue from fronds of the common kelp (*Laminaria*) and measuring their electrical conductivity in various solutions. Under the conditions of these experiments an increase or decrease of conductivity denotes a corresponding increase or decrease of permeability.

Upon transferring the living tissue from sea water to pure sodium chloride of the same conductivity (and at the same temperature) an immediate increase of conductivity was observed. The conductivity continued to increase at a regular rate for about two hours. At the end of this time the conductivity of the tissue was equal to that of the same amount of sea water. At this point it remained stationary even when the tissue was replaced in sea water. This signifies that the tissue was dead.

In this case we are dealing with an irreversible change in permeability. It is natural to ask whether this change is not, up to a certain point, reversible. In order to test this, fresh living tissue was transferred from sea water to sodium chloride of the same conductivity (and at the same temperature); readings were then taken at intervals of two minutes. In the course of five minutes the resistance had fallen from 1,000 ohms to 850 ohms.[3] The tissue was then replaced in sea water and readings were taken at intervals of five minutes. In the course of five minutes the resistance rose to normal and remained unaltered until the following day, when the experiment was discontinued. This experiment was repeated many times under different conditions and with a variety of salts. The results were similar throughout.

In order to make certain that no injury resulted from the treatment with sodium chloride an experiment was performed to ascertain the effect of repeated treatments on the same lot of tissue. In one experiment the tissue was treated with sodium chloride until the resistance dropped from 1,020 ohms to 890 ohms and was then replaced in sea water, after which the resistance rose to 1,020 ohms; this was repeated daily on the same lot of tissue for fifteen days. On the tenth day the tissue began to show a falling off in resistance, which continued to the fifteenth day, when the experiment was discontinued. As this falling off was also shown by the control, which was kept in sea water throughout the experiment, it was not due to the sodium chloride, but to other causes.

The objection may be made that in this experiment the increase in conductivity was due to an increase in the number of sodium ions and that these may normally penetrate the cell more easily than the other ions of the sea water: it might therefore be unnecessary

[1] Dr. McGee died on September 5, 1912.—*Editor.*

[1] For a recent summary see Höber, "Physikalische Chemie der Zelle und Gewebe," Kap. 7 und 10, Dritte Auflage, 1911.

[2] SCIENCE, N. S., XXXV., p. 112, 1912.

[3] All the figures in this paper refer to readings taken at 18° C.

to assume any alteration in the normal permeability of the protoplasm. This supposition can not be correct, for experiments showed that the other ions of the sea water penetrate with about the same rapidity as those of sodium chloride, but in order to be absolutely sure of this point it was tested by employing in place of sea water a solution composed of 1,000 c.c. NaCl .52M plus 20 c.c. $CaCl_2$ .278M. In this solution the proportion of sodium ions to calcium ions is about 100 to 1, as is evident from the fact that both the .52M NaCl solution and the .278M $CaCl_2$ solution have the same conductivity (which is the same as that of the sea water). In this solution the conductivity of the tissue is about the same as in sea water. If we now transfer to NaCl .52M there will be an increase of about 2 per cent. in the number of sodium ions. Consequently (on the supposition that sodium ions penetrate more easily than the other ions of sea water) we may not expect an increase of more than 2 per cent. in the conductivity as long as the permeability remains unaltered. But if the increase is more than 2 per cent. it signifies a corresponding increase in permeability.

In the mixture of 1,000 c.c. NaCl .52M plus 20 c.c. $CaCl_2$ .278M the tissue was found to have a resistance of 1,020 ohms: after two hours the resistance was unaltered. The material was then transferred to NaCl .52M and left until the resistance fell to 860 ohms. It was then replaced in the mixture of NaCl and $CaCl_2$: the resistance soon rose to 1,020 ohms and remained unaltered for several hours; it was left in the mixture over night and on the following morning the resistance was still the same. It subsequently remained the same as that of the control which was kept in sea water throughout the experiment.

In order to find out how much of the resistance is due to living protoplasm the tissue was killed by exposing it for ten minutes to 2 per cent. formalin in sea water;[4] the resistance fell to 320 ohms. On subtracting this from the resistance observed when the tissue is alive we obtain approximately the resistance due to the living protoplasm; this may be called for convenience the *net resistance,* while the resistance before the subtraction is made may be called the *gross resistance.* The net resistance in this experiment was accordingly $1{,}020 - 320 = 700$ ohms before treatment with NaCl and $860 - 320 = 540$ ohms after treatment with NaCl; the net conductance before treatment with NaCl was therefore $1 \div 700 = .001428$ mho. and after treatment with NaCl $1 \div 540 = .001852$, a gain of 29.7 per cent. (the gain in gross conductance was 18.6 per cent.).[5]

It is therefore evident that there has been a very marked increase in permeability which is completely reversible.

Electrolytes may also cause a reversible decrease in permeability. The simplest way of demonstrating this is by means of the following very striking experiment. The resistance of a cylinder of living tissue in sea water was found to be 750 ohms. It was tested an hour later and found to be the same. Sufficient lanthanum nitrate was then added in solid form to make its concentration[6] in the sea water about .01M. After five minutes the resistance rose to 900 ohms. As the conductance of the dead tissue was found (at the end of the experiment) to be 315 ohms, the net resistance before the addition of lanthanum was $750 - 315 = 435$ ohms and the net conductance $1 \div 435 = .0023$ mho. After treatment with lanthanum nitrate the net resistance was $900 - 315 = 585$ ohms and net conductance $1 \div 585 = .001709$, a loss of 25.6 per cent.

[4] Check experiments showed that killing in this way has the same effect on the resistance of the tissue as killing it by means of heat or by iodine vapor or by allowing it to die a natural death.

[5] Owing to the fact that the cylinder of tissue was of the same size in each set of experiments a calculation of the specific resistivity and of the specific conductivity was unnecessary.

[6] The concentration was reduced by the precipitation of a small amount of lanthanum sulphate: this had practically no influence on the subsequent result, since the outcome is the same if we use in place of sea water a mixture of 1,000 c.c. NaCl . 52M + 20 c.c. $CaCl_2$. 278M, in which case no precipitate is formed. It should be noted that the addition of lanthanum chloride has the same effect as the addition of lanthanum nitrate.

In order to ascertain whether this change in permeability is reversible the tissue was replaced in sea water. In the course of an hour its resistance returned again to the original condition.[7] The experiment was then repeated three times on the same lot of material with the same result; it was then allowed to stand over night in sea water. On the following day there was no appearance of injury and its resistance was the same as that of the control which had remained in sea water throughout the experiment. The tissue was then placed in the sea water plus lanthanum and left until its resistance had increased about 150 ohms; it was then put back into sea water and left until the resistance fell to normal. This was repeated three times and the tissue was then allowed to stand over night in sea water. On the third, fourth and fifth days the same experiment was repeated four times. On the fifth day the tissue appeared to be in as good condition as the control and had a resistance which was slightly higher. There was therefore no reason to suspect that the changes in permeability had been attended by any injurious effect.

Similar experiments were performed in which calcium chloride was used in place of lanthanum nitrate. In this case 3.3 gm. anhydrous $CaCl_2$ were added to each 1,000 c.c. of sea water. Owing to the fact that the rise in resistance took place more slowly than when lanthanum was used, the experiment was performed twice on each of the five successive days. On the sixth day the material was in as good condition as the control and had the same resistance.

It is therefore evident that the permeability may be greatly decreased and then restored to the normal several times on five successive days without any trace of injury. Further experiments showed that the permeability may be alternately increased and decreased twice daily for five days without injury. The amount of increase and decrease was about the same as in the experiments just described.

[7] If the material is left in sea water plus lanthanum nitrate the increased resistance is maintained for a long time unaltered.

Experiments on dead tissue (killed by heat or by formalin or allowed to die a natural death) showed that the results described above are due entirely to the living cells.

A very marked decrease of permeability may be produced by a considerable variety of other salts.

The addition of these salts in solid form simultaneously increases the conductivity of the solution and decreases the conductivity of the tissue. This affords the most convincing proof that the change in the conductivity of the tissue in these experiments can not be due to any cause other than a change in permeability; for the concentration of the ions of the sea water remains unchanged, and if they were able to penetrate as freely as they did before the addition of the salt the resistance would not increase. It would, in fact, diminish on account of the increased conductivity of the solution held in the cell walls, as is clearly shown by experiments on dead tissue.

It may be remarked incidentally that these experiments effectually dispose of the possible objection that the current passes between the cells but not through them. Were this objection well founded the decrease in conductivity could be explained only as the result of a decrease in the size of the spaces between the cells. This decrease could not be brought about except by greatly reducing the thickness of the cell walls. Both macroscopic and microscopic measurements show most conclusively that this does not occur. The contrary effect would be produced by the addition of salts in solid form, for they would tend to produce plasmolysis and thereby to increase the space between the cells.

Results.—1. It is possible to cause rapid and very large changes in permeability by means of electrolytes.

2. These changes may consist in either an increase or a decrease in permeability.

3. Within wide limits these changes may be completely reversible and entirely devoid of injurious effects.

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